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Physiology & Behavior 86 (2005) 731 – 746

PHYSIOLOGY & BEHAVIOR

Memory inhibition and energy regulation

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Received 22 July 2005; received in revised form 25 August 2005

Abstract

At a simple behavioral level, food intake and body weight regulation depend on one's ability to balance the tendency to seek out and consume food with the ability to suppress or inhibit those responses. Accordingly, any factor that augments the tendency to engage in food seeking and eating or that interferes with the suppression of these behaviors could produce (a) caloric intake in excess of caloric need; (b) increases in body weight leading to obesity. This paper starts with the idea that excess body weight and obesity stem from a failure or degradation of mechanisms that normally function to inhibit eating behavior. Unlike previous approaches, we focus not on failures of traditional physiological (e.g., neural, hormonal) regulatory control mechanisms, but on disruptions of inhibitory learning and memory processes that may help to regulate energy intake. This view of energy dysregulation as a type of "learning disorder" leads us to the hippocampus, a brain structure that has long been regarded as an important substrate for learning and memory and which we think may be critically involved with a specific type of memory inhibition function that could contribute to the suppression of food intake. With this focus, the search for environmental origins of the current obesity epidemic in Western populations is directed toward factors that alter hippocampal functioning. We conclude by offering a preliminary account of how consumption of foods high in saturated fats might lead to impaired hippocampal function, reduced ability to inhibit caloric intake and, ultimately, to increased body weight.

Keywords: Hippocampus; Inhibition; Obesity; Food intake; BDNF

Longitudinal data show that, after a long period of relative stability, the incidence of overweight and obesity in the United States began to increase in the 1980s and has continued to increase to the present day (e.g., Flegal, this issue). Adjusting for age and height, there has been nearly a 10% increase in mean body weight during this period, and the rate of obesity has almost doubled [1]. This alarming trend toward weight gain is apparent, in varying degrees, across all age groups, ethnic groups, and social strata, in all regions of the country [2]. As might be expected based on these figures, both food supply and dietary survey data indicate that energy intake in the United States has also been on the rise (see [3] for review). For example, by some estimates, caloric intake in 1994 was 500 kcal/day higher than in 1977 [4].

The unprecedented speed and magnitude at which these increases have occurred suggest that the current obesity "epidemic" has environmental, rather than solely biological origins. Prominent on the list of potential environmental causes of recent increases in overweight and obesity are increased availability, energy density, portion sizes and affordability of food [5,6], rising consumption of soft drinks [7], convenience foods [8], and reduced energy expenditure [9]. These factors combined with the development and mass implementation of sophisticated marketing techniques designed to entice consumption have contributed to what some researchers term an "obesigenic" environment [10] that has overwhelmed the biological regulatory systems that normally control caloric intake (see Blundell, Levitsky, Levin, and Popkin et al., this issue).

How have changes in the food environment come to overwhelm our regulatory control systems? One answer to this question suggests that our biology may be better suited for promoting than for inhibiting eating (e.g., [11]). As Prentice

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doi:10.1016/j.physbeh.2005.09.004

(this issue) notes, famine has been a pervasive threat to survival throughout much of human history—so pervasive that most, if not all of us, are likely to have ancestors that survived famine. Although inheriting traits that helped our ancestors to survive famine would presumably improve our own chances for survival in the face of extreme food scarcity, these same characteristics might also promote excessive intake and body weight gain under the current conditions of food abundance.

It has also been suggested that learned relationships between food-related environmental stimuli and the rewarding consequences of eating enable food cues to promote energy intake in excess of regulatory needs (Woods, Levin, this issue). Thus, in the current environment in which food and food-related stimuli are abundant, this type of learned evocation of eating might contribute significantly to caloric intake and weight gain. Several papers in the volume (e.g., Holland and Petrovich; Balleine; and Kelley) share the goal of identifying the neural substrates and processes (e.g., motivational, reinforcement, associative) that underlie the learned evocation of nonregulatory food intake. Furthermore, there is considerable evidence that animals encode information about postingestive nutritive consequences of eating and about the nature of the orosensory stimuli that predict those consequences (e.g., [12]). According to Swithers and Davidson (this issue), the entry into the food environment of products in which orosensory features and caloric content are dissociated could interfere with the ability to encode or utilize appropriate food–calorie relationships and this interference might produce energy dysregulation leading to obesity.

The purpose of the present paper is to consider further the role of learning and memory processes in food intake and body weight control, with special emphasis on the questions of (a) how interference with these processes might lead to energy dysregulation, (b) how changes in the food environment could contribute to this interference. It may seem that memory impairments would have little in common with impaired regulation of intake and body weight. Yet, based on new data and on new interpretations of older findings, a number of intriguing links between memory and the control of energy intake are beginning to emerge. At the center of this developing picture is the hippocampus, a brain structure long considered to be an important substrate for learning and memory. Several relatively recent findings and conceptual developments point to possible interdependency between memory functions performed by the hippocampus and regulatory functions that are thought to involve other regions of the brain.

The process of matching energy intake to energy expenditure involves a complex physiological system that monitors both short-term and longer term fluctuations in bodily energy resources (e.g., [13,14]; Woods, this issue; Powley this issue). These fluctuations are presumed to produce signals that, when detected by the brain, modulate the performance of food-seeking and eating behaviors that enable animals to maintain energy homeostasis. We begin this paper by presenting a conceptual framework which describes how physiological satiety signals might engage learning and memory mechanisms to exert an inhibitory influence on appetitive and eating behaviors. We then describe recent data and theory which suggests that the hippocampus is a brain substrate for the type of inhibitory memory mechanisms that mediate the behaviorally suppressive effects of satiety cues. This section examines the possibility that hippocampal damage impairs the ability to inhibit activation of prepotent reward memories by environmental cues—producing a type of 'hypermnesia' with respect to the tendency to remember rewarding events. Next, we review findings indicating that the efficient inhibitory control of food intake and body weight gain also require an intact hippocampus. Finally, we consider how dietary features of the current obesigenic food environment could promote hippocampal dysfunction leading to a cycle of impaired inhibition, overeating, and further hippocampal dysfunction.

1. Behavioral inhibition and energy regulation

Food intake and body weight regulation depend on one's ability to balance the tendency to seek out and consume food on some occasions with the ability to suppress or inhibit those responses at other times. This type of modulation is made easier for animals because the postingestive consequences of eating are not always the same. To paraphrase Balleine (this issue), for any organism, the biological significance of the stimulus consequences of eating can be defined in homeostatic terms; i.e., in terms of their ability to minimize deviations from a physiological set point. We take this to mean that under conditions of negative energy balance, eating and appetitive behaviors produce the rewarding effects of returning to homeostasis, whereas after homeostasis has been achieved, these behaviors no longer produce rewarding postingestive outcomes, but are instead followed by nonrewarding consequences produced by movement away from homeostasis (i.e., positive energy balance).

There is no reason to doubt that animals learn to anticipate both of these outcomes. That is, under conditions of negative energy balance, food and food-related environmental events should become associated with rewarding postingestive stimulation (e.g., pleasant post-oral sensations). Based on this association, the food cues should excite or activate the stored representation of that reward (i.e., its memory) on subsequent occasions. Based on simple Pavlovian conditioning principles, activation of that memory by environmental cues would promote appetitive and consummatory responding that produced the rewarding stimulation in the past. On the other hand, animals that have achieved homeostasis would experience food cues that are no longer followed by the rewarding postingestive outcome. Under these circumstances, animals would learn to inhibit the ability of the food cues to excite or activate the reward memory, thereby inhibiting the ability of these food cues to evoke the conditioned eating and appetitive behaviors that produce that reward [15,16].

1.1. Occasion setting and intake regulation

The set of stimulus-event relations outlined above describe what we have termed an "occasion setting" model of intake

regulation [17–19]. In the laboratory, arbitrary stimuli can be established as occasion setters based on training within certain types of conditional discrimination problems (see [20] for review). For example, serial feature negative discriminations take the general form A+, X→A−, where target conditioned stimulus A (e.g., a tone) is followed by reinforcement (e.g., a food pellet) when presented alone on A+ trials, but is not followed by reinforcement when it is preceded by the presentation of the feature stimulus X (e.g., a light) on X→A− trials. Animals show they have solved this problem when they exhibit more conditioned responses on A+ than on X→A− trials (e.g., [21–23]). Feature stimulus X is referred to as a negative occasion setter, because its absence is informative about or 'sets the occasion' for the reinforcement of stimulus A. It is possible to establish punctate cues or longer duration, diffuse contextual stimuli as negative occasion setters, based on training them as features in feature negative discrimination problems (e.g., [24]). Furthermore, the results of many studies indicate that relatively long duration, interoceptive stimuli, such as those arising from different deprivation conditions or produced by drugs can be established as occasion setters (e.g., see [18,25–29]).

One current line of thinking about the neurohormonal basis of energy regulation seems to lend itself to interpretation as an example of negative occasion setting. According to Woods and Seeley ([30]; also Woods, this issue), eating is usually initiated at times that are convenient or habitual and is thus based more on learned environmental cues than on internal bodily signals of energy need. Because meal initiation is considered to be under environmental control, meal size or amount eaten is viewed as the regulated parameter most critical to maintaining energy balance (also see Smith [31]). With the exception of emergency conditions produced by extreme energy depletion, Woods suggests that animals do not rely on internal energy depletion or hunger signals to inform them that they need to find food and initiate eating. Rather, intake regulation depends on the detection of hormonal "satiety" signals that terminate meals when enough food has been consumed to restore energy balance. For example, cholecystokinin (CCK), a hormone secreted from the duodenum in response to nutrients in the lumen is prominent on the list of potential satiety signals [32,33]. Thus, energy regulation depends on the control of meal size by signals with interoceptive sensory consequences that correspond to satiety or fullness.

Although we seem to know much about how food intake leads to the production of satiety signals, and we know something about how these signals might give rise to the distinct sensory consequences of satiety (e.g., by producing gastric distention [34,35]), details are lacking about precisely how the sensory consequences of satiety produce meal termination and how they suppress eating until the beginning of the next meal. For example, to produce meal termination satiety signals must act to inhibit or suppress the continued evocation of eating by environmental cues. Some accounts have attempted to address this problem with reference to motivational processes (e.g., see [36] for recent review). One possibility is that satiety reduces the reward value of food and reduces the ability of environmental cues to motivate appetitive behavior and eating. Conversely, appetitive and eating behavior may be motivated by the enhanced reward or incentive value of food and cues associated with food that emerges under conditions of negative energy balance. Unfortunately, the physiological or psychological mechanisms that link energy balance to motivation and that link motivation to intake and appetitive behavior have not yet been specified with enough detail to provide more than a descriptive account of energy dysregulation. Current research aimed at specifying these links holds promise for developing an experimental analysis of how motivational processes might contribute to excess food intake and body weight gain (e.g., see Kelley, this issue; Balleine, this issue; Holland and Petrovich, this issue [37]).

Fig. 1 depicts how satiety signals could function as negative occasion setters within a "naturally occurring" feature negative discrimination problem. As shown in that figure, food cues encountered in the absence of satiety signals predict the occurrence of a rewarding postingestive outcome (equivalent to A+ trials in a feature negative problem), whereas food cues encountered in the presence of satiety signals indicate that rewarding outcome will not occur (equivalent to X→A− trials in feature negative discriminations). Only in the absence of satiety signals will animals experience the rewarding postingestive consequences of eating. Pre-oral environmental and orosensory food cues can become embedded in an excitatory association with the memorial representation of that rewarding experience. When satiety signals are present, food cues are not followed by the rewarding postingestive outcome, resulting in the formation of a concurrent inhibitory association between the food cues and the representation of the postingestive reward. Thus, satiety signals act as negative occasion setters by predicting that food cues will not be accompanied by postingestive reward. In this role, satiety signals gate the activation of inhibitory associations that have formed between food cues and the memory of postingestive reward. This enables satiety signals to prevent environmental and orosensory food cues from continuing to

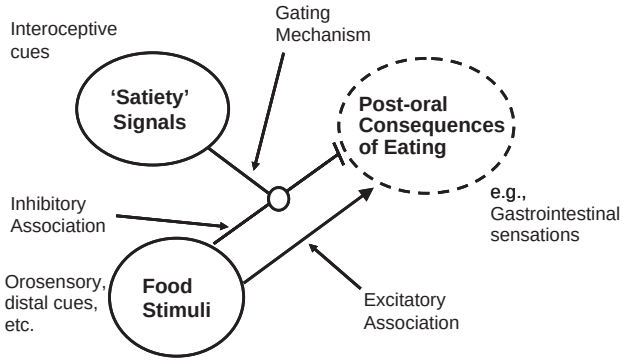

Fig. 1. An occasion setting model of food intake regulation. Satiety signals are depicted as gating an inhibitory association that serves to suppress activation of the memory of the rewarding postingestive sensory consequences of eating food.

evoke appetitive and eating behavior by reducing the ability of these cues to excite the memory of the rewarding postingestive consequences of eating.

2. Another look at the substrates of energy regulation

Much research on the causes of overeating and excessive weight gain has been directed at identifying the brain regions where metabolic and hormonal signals that stimulate or suppress intake are detected and utilized. The hypothalamus has received the most attention by far as a substrate for the control of food intake and body weight regulation. Early interest in the hypothalamus stemmed from findings that dramatic elevations or reductions in eating and body weight could be produced by lesioning specific hypothalamic nuclei [38]. More recently, many studies have identified the hypothalamus, especially the arcuate nucleus, as a target for neuropeptide signals that can produce marked changes in eating and body weight when manipulated experimentally (e.g., [30,39]). A literature search reveals that since the mid-1960s, several thousand reports have been published investigating the potential role of various hypothalamic nuclei in the regulation of food intake and body weight.

Unfortunately, clear links between the function of the hypothalamus and current alarming increases in the incidence of obesity in the general population have not yet been identified. For example, relatively few cases of being overweight or obese in humans seem to involve hypothalamic pathologies or malfunctioning hypothalamic signaling systems [40,41]. Thus, although surgical, genetic, and pharmacological manipulations of the hypothalamus can have profound effects on energy regulation in laboratory settings, it is not yet certain that the reduced regulatory control that is currently occurring outside of the laboratory will be traced to alterations in hypothalamic functioning. According to Berthoud (e.g., [40]), the realization that, in common obesity, there is "nothing wrong" with physiological regulatory control systems should encourage further exploration of the links between cognitive and metabolic controls of intake.

One implication of the occasion setting model presented in Fig. 1 is that important controls of energy regulation exist outside of the hypothalamus in areas of the brain that are involved with learning and memory processes, especially those processes involved with negative occasion setting and more generally with memory and behavioral inhibition. The hippocampus, a structure comprising pyramidal cells CA3, CA2, CA1 and the hilar and granule cells of the dentate gyrus that is located bilaterally within the medial temporal lobes of the brain [42], seems to be involved with these processes. In this section, we review research and theory suggesting that memory inhibition is an important function that depends, in both human and nonhuman animals, on the hippocampus. After examining evidence that the hippocampus may be involved with the type of inhibitory learning and memory processes depicted in Fig. 1, we will consider how the hippocampus might gain access to bodily signals that it could use to enter into the inhibitory control of food intake and we will review behavioral findings that demonstrate a link between the hippocampus and energy regulation.

2.1. The hippocampus and memory inhibition in humans

Modern interest in the hippocampus began in the early 1950s when neurosurgeons performed an experimental operation on an epileptic patient known as H.M. that removed the hippocampus and other parts of the medial temporal region on both sides of his brain. Although this procedure brought H.M.'s seizures under control, it also produced a near complete loss of his ability to form new memories [43]. The severe anterograde amnesia exhibited by H.M. focused much attention on the role of the hippocampus in learning and memory. For example, research on Alzheimer's disease (AD) and on other disorders (e.g., stroke) that include memory impairment as a signature symptom have often regarded the hippocampus as a key site of neurodegeneration [44,45].

There have been many ideas about how to best conceptualize the learning and memory processes that rely on the hippocampus. Most views have either identified the hippocampus with encoding certain types of information (e.g., memories for events, memories for locations of objects in space, e.g., [46,47]) or with the performance of certain types of information processing functions (e.g., formation of stimulus configurations; flexible use of memory representations [48,49]). Consistent with the occasion setting model depicted in Fig. 1, recent descriptions of human memory processes point out that adaptive memory functioning involves not only encoding and retrieving of desired or appropriate information but also the suppression of associations or memories that are not appropriate in a given context or set of circumstances (e.g., [50,51]). For example, changing one's computer password is usually accompanied, for a least a short time, by a number of annoyingly futile attempts to use the old password. Remembering to use the new password improves as the ability of the screen prompt to activate the memory of the old password grows weaker. Recent research on human cognition indicates that this type of forgetting is not a passive side effect of encoding new memories, but is instead the result of the recruitment of an inhibitory process that overrides the activation of prepotent memories and the behaviors that they produce. The forgetting induced by this type of inhibition is therefore highly beneficial, limiting the tendency for retrieval of outdated or inappropriate memories to disrupt adaptive performance [50,52].

Of special interest are recent findings indicating that the ability of humans to inhibit inappropriate memories involves the hippocampus. Anderson et al. [53] used what is termed a "think/no-think" paradigm in conjunction with functional magnetic resonance imagery (fMRI) to study whether there were brain regions in which activation predicted individual differences in the capacity to inhibit unwanted memories. With this design, healthy human subjects learned word-pairs (e.g., ordeal-roach) before performing the think/no-think task while being scanned. This task involved trials where the stimulus component of a word-pair was presented (e.g., ordeal) and the

subjects were either asked to recall and think about the response component (e.g., roach) or to try to prevent the response word from entering consciousness during the period that the stimulus word was presented.

After scanning, the ability of the subjects to use the original cue to retrieve the response term was assessed for words that had been presented under the think and no-think conditions, and for baseline words that had not been cued during scanning. Memory for suppressed terms was found to be impaired compared to baseline terms, indicating that no-think training had the effect of inhibiting memorial processing of suppressed words. More importantly, different patterns of hippocampal activation were found for words trained in the no-think and think conditions, depending on whether those words were remembered or forgotten during the subsequent recall test. For the no-think condition, hippocampal activation was increased for response terms that were forgotten during the subsequent recall test compared to words that were remembered. For words trained in the think condition, the opposite pattern of activation was observed (i.e., hippocampal activation was reduced). This outcome indicates that the success of attempts not only to excite, but also to inhibit the activation of items in memory, is correlated with different levels of hippocampal activation. Thus, these findings indicate a role for the hippocampus in suppressing the retrieval of unwanted memories.

One implication of this interpretation is that reduced ability to suppress prepotent or inappropriate memories and the reactions they evoke might be a consequence of hippocampal dysfunction. It is worth noting that impaired memory inhibition has been related to hippocampal pathology (e.g., structural and electrophysiological abnormalities) that is symptomatic of both schizophrenia (e.g., [54]) and Alzheimer's disease [55]. For example, McCarley et al. [56] suggested that many of the cognitive symptoms of schizophrenia can be understood as "disturbed suppression of associations", and "failure to inhibit" prepotent associations that might be linked to interference with recurrent inhibition in the hippocampus. Similarly, increased recall intrusion errors have been reported to occur during the early stages of Alzheimer's disease (AD). Dalla Barba and Wong [57] found that patients diagnosed with AD that had studied lists of items from various categories showed relatively few intrusion errors (i.e., naming items that were not on the studied list) when asked to freely recall as many items as possible, but showed many intrusion errors when recall was cued with category names (e.g., naming types of fruits that were not on the studied list, when cued with the category name "fruit"). The finding that memory intrusions are most likely to occur in the presence of strong retrieval cues suggests that normal inhibition or suppression of retrieval of inappropriate memories is impaired as a consequence of hippocampal damage that occurs during the early stages of AD (e.g., [58,59]).

2.2. Hippocampal memory inhibition in nonhuman animals

The idea that a function of the hippocampus is to suppress unwanted or inappropriate memories has also been suggested by the results of animal lesion studies. Gray and McNaughton [60,61] reported that in a variety of situations, rats with the hippocampus removed appear to have difficulty appropriately resolving conflicts between competing response tendencies involving the same goal event. For example, if a response that previously produced food is subsequently nonrewarded or punished, rats with hippocampal damage are less able than controls to learn to refrain from making the response. According to Gray and McNaughton, both positive and negative value can be attached to a goal. The hippocampus is needed for rats to assign negative value to the goal and thus to reduce the capacity of the goal object and stimuli that are associated with that object, to promote performance. Because removing the hippocampus interferes with the assignment of negative value, the memory of the positive value of the goal will continue to evoke, now inappropriate, conditioned responding. Gray and McNaughton describe this effect of hippocampal damage as 'hypermnesia' and claim that, in contrast to many views of hippocampal function, poor memory performance by rats without a hippocampus occurs because they remember too much rather than too little.

A similar model developed within our own laboratory (e.g., [62,63]) describes hippocampal mediation of such conflicting response tendencies in largely associative terms. According to this view, the hippocampus may be needed to form and utilize inhibitory associations among stimuli and outcomes that are already embedded in excitatory associations with one another. For example, whereas training a cue as a signal for a reward would embed that cue in an excitatory association with that outcome, subsequent extinction training of that cue (i.e., presenting it without reward) would put the cue in a concurrent inhibitory association with reward that would then oppose response elicitation based on the excitatory association. We proposed that the hippocampus is needed to form and utilize the inhibitory link between the cue and consequence. Accordingly, hippocampal damage would be expected to interfere with inhibitory association formation, thereby making it more difficult for the animal to suppress the memory of reward and extinguish conditioned responding.

Our view, in agreement with Gray and McNaughton, suggests that rats without a hippocampus remember too much because they are impaired in the ability to suppress the activation of inappropriate information. Accordingly, like Gray and McNaughton, we predict the effects of hippocampal lesions to be greatest in behavioral tests where performance depends on the ability of rats to suppress the excitement of previously formed memories elicited by the same conditioned cue.

We recently described the results of a study that confirms these predictions [63]. This experiment tested rats that had received selective ibotenate (IBO) lesions of the hippocampus. IBO lesions produce complete destruction of hippocampal cells with little or no damage to adjacent structures (e.g., subiculum, entorhinal cortex), to fibers of passage (axons of neurons that pass through the hippocampus), or to afferents that terminate in the area. Also important, the underlying vasculature is spared [64,65]. In addition, rats with IBO hippocampal lesions show no gross behavioral alterations relative to intact controls. This

type of neuroanatomical and behavioral selectivity is usually not found with older, conventional (e.g., aspiration, electrolytic, radiofrequency) lesioning techniques (see [66] for a review).

Following recovery from surgery, the IBO-lesioned rats and their controls were trained to solve a simple discrimination problem in which one conditioned stimulus was followed by the presentation of reward (CS+) and a different conditioned stimulus (CS−) was not. The top panels of Fig. 2 show that lesioned rats (top-right panel) were not impaired relative to intact controls (top-left panel) in solving this simple discrimination problem. These results confirm that selective removal of the hippocampus had no obvious effect on the ability of rats to learn about a cue that signaled reward or to refrain from responding to a cue that did not signal reward.

Next, both groups received discrimination reversal training where the identity of the rewarded and nonrewarded cues was reversed. As indicated in the bottom panels of Fig. 2, significant discrimination reversal learning was exhibited by control rats but not by hippocampal-lesioned animals at the end of 12 sessions of reversal training. The results showed that reversal performance for rats without a hippocampus was not impaired with respect to responding to the former CS−, but that IBO-lesioned rats persisted more than controls in their tendency to respond to the former CS+. The finding that rats without a hippocampus are impaired in their ability to refrain from responding to a previously rewarded cue is consistent with the idea that the hippocampus is needed to inhibit the response evoking power of cues that have been associated previously with reward. Other findings related to hippocampal involvement in inhibitory learning and the assignment of affective value to goal events are reviewed by Gray and McNaughton [60], Chan et al. [62], McNaughton and Wickens [61], and Davidson and Jarrard [63].

2.3. Hippocampus and negative occasion setting

The findings discussed above provide evidence that the hippocampus plays a role in the learning of inhibitory associations among cues and outcomes that are already linked by an excitatory association. Review of Fig. 1 will show that this type of association formation is seen as critical to the development of negative occasion setting. Thus, one would expect that rats without a hippocampus would also show an impaired ability to inhibit responding on nonrewarded trials in feature-negative discrimination problems. This outcome has been reported by Holland et al. [67]. Rats with selective

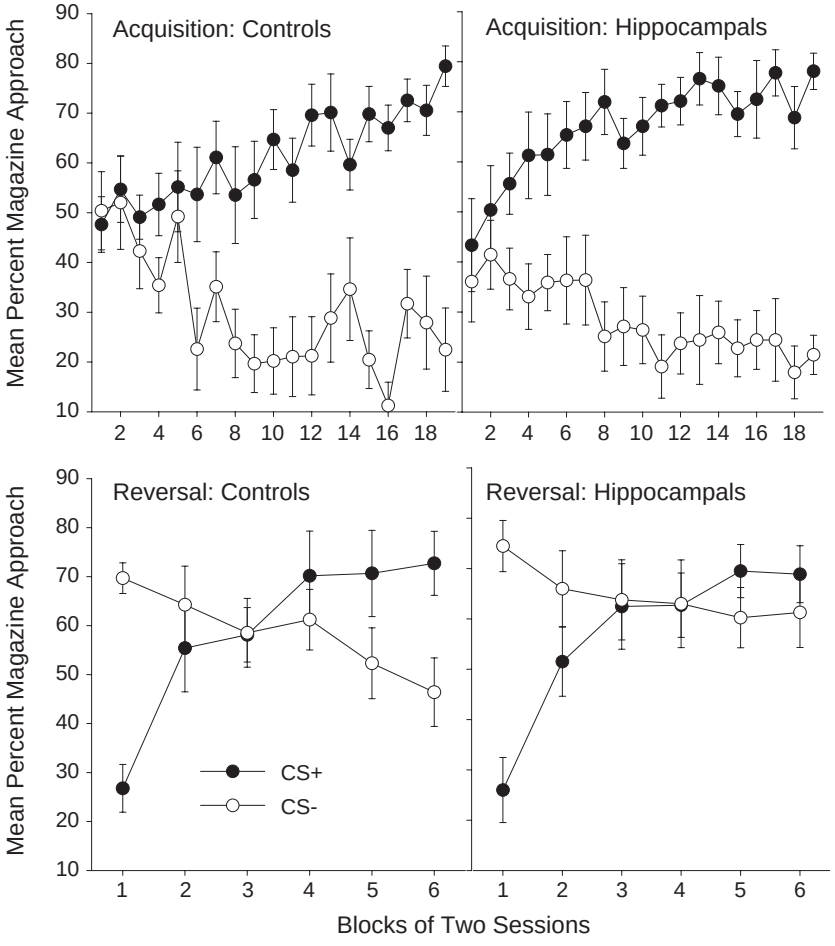

Fig. 2. Effects of hippocampal lesions on the acquisition and reversal of a simple discrimination problem. Rats with IBO lesions of the hippocampus (top-right panel) were unimpaired relative to controls (top-left panel) during acquisition of a simple Pavlovian discrimination. In contrast, lesioned rats (bottom-right panel) were impaired relative to controls (bottom-left panel) during subsequent discrimination reversal training.

neurotoxic lesions of the hippocampus responded like controls on rewarded A+ trials of the feature-negative problem, but responded significantly more than controls on nonrewarded X→A− trials.

Holland et al. also noted that removing the hippocampus increased general activity evoked by diffuse context cues in the training environment during periods when neither the feature nor the target CS were present. Because contextual cues are thought to become associated with reward at the outset of training before undergoing subsequent extinction, over-responding to context cues may be another example of failure of inhibitory learning by rats with hippocampal lesions (also see [68]). Moreover, Bouton [15] proposed that context stimuli can function as negative occasion setters in situations involving training and subsequent extinction or counterconditioning (e.g., initial training with reward, followed by continued training with an aversive outcome) of a punctate cue. In these situations, contexts acquire occasion setting power to the extent that they provide information about which type of outcome is most likely to occur. Thus, occasion setting functions can be performed by diffuse, relatively long duration cues, in addition to punctate stimuli.

2.4. Summary

Although the hippocampus has long been regarded as a brain substrate for learning and memory, specification of the types of learning and memory functions that depend on this structure continues to be an important research goal. New ideas about the operation of associative memory systems identify successful memory retrieval not only with the activation of appropriate or target memories, but also with the inhibition of competing or unwanted memories. Recent fMRI findings suggest that the hippocampus may be a critical component of the brain system that performs this inhibitory function. One source of converging evidence for this possibility is provided by reports that both hippocampal pathology and an inability to suppress unwanted or inappropriate memories occur during the early stages of both schizophrenia and Alzheimer's disease. In addition, nonhuman animals with highly selective hippocampal lesions exhibit, in a variety of test situations including feature-negative discrimination problems, a reduced ability to refrain from responding to cues that have been previously associated with reward. Such findings suggest a role for the hippocampus in suppressing reward memory activation or in reducing the capacity for rewards or the memories of reward to accrue negative affective value. Based on these results, it is at least conceivable that reduced inhibitory control of appetitive behavior (which presumably involves highly salient memories of food rewards) and ultimately of caloric intake regulation might also be a consequence of impaired hippocampal functioning.

3. The hippocampus and satiety signals

Thus far, we have suggested that the ability of satiety signals to inhibit eating and appetitive behavior may be based at least in part, on the establishment of these signals as natural negative occasion setters. In this capacity, satiety signals modulate feeding behavior by inhibiting the excitation or retrieval of reward memories by conditioned food stimuli. We also suggested that memory inhibition processes like those involved with negative occasion setting operate in both human and nonhuman animals and involve the hippocampus in both species. If these two suppositions are correct, then one should anticipate that the hippocampus would play a role in the inhibition of food intake. An important step toward evaluating this latter hypothesis is to consider whether or not the hippocampus has access to satiety signals that could function as occasion setters.

3.1. Neuroanatomical connections

The hippocampus can be divided anatomically and perhaps functionally, along the septo-temporal axis [69]. Specifically, the major input from sensory cortices projects primarily to the dorsal two-thirds of the hippocampus by way of the association cortex and entorhinal and perirhinal cortices [70–72]. Thus, the dorsal hippocampus (DH) receives highly processed information from all sensory systems. In contrast, the ventral hippocampus is anatomically more closely associated with subcortical areas, especially to hypothalamic [73], neuroendocrine and preautonomic cell groups of the periventricular zone [74], which includes a set of interconnected hypothalamic nuclei intimately involved in the control of ingestive functions [75,76]. Among these is the arcuate nucleus, which, as noted previously is the site of receptors for many circulating neuropeptides related to food intake, including those thought to function as longer term signals of body adiposity (see below).

The hippocampus also has access to signals that are carried to the nucleus tractus solitarius (NTS) in the caudal brainstem via vagal afferents and by afferent fibers passing into the spinal cord from the upper gastrointestinal tract [77]. The NTS appears to be one area where meal-related cues produced during ingestion by oral taste stimulation and by nutrient stimulation from the gastrointestinal tract are integrated to inhibit intake (e.g., [78]). Several multisynaptic pathways have been identified that connect brainstem feeding control areas to both dorsal and ventral areas of the hippocampus (e.g., [14,69,79]). In addition, the hippocampus also has direct links to the so-called limbic "motive circuit" that includes nucleus accumbens, a structure thought to be a substrate for reward, and the amygdala, a structure with nuclei that are involved with information processing and with the processing of metabolic, especially lipoprivic signals [40]. The functional role of these neural connections has not yet been clearly elucidated.

3.2. Neurohormonal connections

In addition to neural routes of communication that connect the hippocampus to hypothalamic, brainstem and other areas linked to the control of food intake, it appears that the hippocampus also has access to neuropeptides that have been

strongly implicated in the inhibitory control of food intake. CCK is perhaps most prominent on the list of intake suppressing hormones. Two types of CCK receptors, labeled CCK-A and CCK-B (or CCK-1 and CCK-2) have been identified, with the feeding inhibitory actions of CCK mediated through its interactions with the CCK-A receptor subtype [80]. Studies with CCK antagonists support this conclusion, as does research with the Otsuka Long Evans Tokushima Fatty (OLETF) rats. OLETF rats lack the CCK-A receptor and are spontaneously hyperphagic, obese, and insensitive to the intake suppressive effect of exogenous CCK [81].

In addition to being found in regions of the brain with specific links to food intake regulation (viz., the nucleus solitary tract (NTS), posterior nucleus accumbens, ventral tegmental area, substantia nigra), CCK-A receptors are abundant in the hippocampus. Furthermore, reports that OLEFT rats show impaired performance on hippocampal-dependent forms of learning [82,83] encourage the hypothesis that CCK not only provides a satiety signal but may also contribute to hippocampal functioning more generally. Other reports show impaired learning and memory following administration of CCK-A receptor antagonists (e.g., [84,85]). It remains to be determined whether these types of impairments occur in all tasks that depend on the hippocampus or only in tasks that are especially designed to assess hippocampal-dependent forms of inhibitory learning.

Receptors for the pancreatic hormone insulin and for leptin, a hormone released from adipose tissue, are abundant in the both hypothalamic arcuate nucleus and in the hippocampus (see [86]). Furthermore, both insulin and leptin appear to modulate the excitability of neurons in both brain areas. These hormones are thought to function as body adiposity signals, as both are secreted in proportion to body fat mass, and thus may provide information about the status of long-term energy stores [87]. Administration of exogenous insulin or leptin directly into the ventricles of the brain produces a dose-dependent decrease in food intake [88,89]. On the other hand, animals that lack or are insensitive to either hormone are hyperphagic and gain weight. This hyperphagia appears to be attributable, in part, to a reduction in the effectiveness of CCK and perhaps other meal-generated satiety signals [30]. There is also evidence that the effects of leptin and insulin on food intake and body weight may involve other neuropeptide signaling systems. For example, the actions of leptin and insulin have been linked to the melanocortin signaling system [90,91] and to attenuation of the production and release of neuropeptide Y (NPY), a potent stimulator of food intake and weight gain [92,93].

While the effects of circulating leptin and insulin on food intake and body weight have been associated with detection by their hypothalamic receptors, both hormones have also been shown to influence learning and memory processes and these effects have been attributed to their influence on the hippocampus. For example, both leptin and insulin have been shown to influence long-term potentiation (LTP) and long-term depression (LTD) processes often considered to be cellular mechanisms for hippocampal-dependent learning and memory (e.g., [94–96]). In addition, Li et al. [97] reported that leptin receptor-deficient Zucker rats and db/db mice showed impaired LTP and LTD that was not reversible by leptin treatment. The performance of these rats on a hippocampal-dependent spatial learning task was also impaired.

A number of studies with human clinical populations have suggested a role for insulin in learning and memory. Cognitive impairments have been reported for humans that suffer from Type I diabetes, which is characterized by insulin deficiency [98]. Type II diabetes, which involves insensitivity or resistance to the effects of circulating insulin, is also associated with cognitive deficits [99]. Furthermore, patients with AD show glucoregulatory disturbances, lower plasma and cerebrospinal fluid levels of insulin, and impaired sensitivity to systemic insulin [100,101]. AD patients also show improved performance on cognitive tasks when their insulin levels are increased to higher than normal levels. However, insulin administration improves performance even at doses that have no effect on glucose levels in the periphery [102]. Of course, there is no direct way to assess the degree to which brain changes resulting from low secretion of, or insensitivity to, insulin were confined to the hippocampus, or to determine if the cognitive impairments were the results of hippocampal changes or are attributable to changes elsewhere in the brain. More direct evidence has been provided by animal studies. For example, injection of streptozotocin (STZ), which induces Type I diabetes by destroying insulin-producing pancreatic cells, impairs performance in several types of learning and memory problems, including hippocampal-dependent spatial learning. These impairments can be reversed by administration of exogenous insulin [103]. Other results show that insulin receptor activity in the hippocampus is upregulated following training on a spatial learning problem [96].

There is clear evidence that CCK, leptin, and insulin are importantly involved with the inhibition of food intake and the control of body weight. However, as indicated above, each of these neuropeptides is abundant, not only in brain areas (hypothalamus, NTS) that have been closely associated with energy regulation, but also in the hippocampus, a brain structure long associated with cognitive processes. Moreover, alterations in the availability of, or sensitivity to, CCK, leptin and insulin impact both energy regulation and learning and memory. It is tempting to speculate that the influence of these, and perhaps other neuropeptides (e.g., ghrelin see [22]) on food intake and body weight depends, at least in part, on their effects on the hippocampus and perhaps other brain regions (e.g., prefrontal cortex [53]), that are involved with inhibitory learning and memory. Evidence related to this hypothesis will be summarized next.

4. Links between the hippocampus and eating and appetitive behavior

Previous studies have shown that damage to the hippocampus, or to brain areas that include the hippocampus, interferes with controls of food intake regulation. Such damage has been reported to (a) reduce or abolish the ability to use information

provided by interoceptive energy state signals; (b) increase the tendency to engage in appetitive behaviors that lead to food; (c) augment food intake; (d) produce heightened general behavioral activity in environments that are strongly associated with food. These findings are reviewed below.

4.1. The hippocampus and food intake regulation in humans

As noted previously, patient H.M. had large portions of his temporal lobes, including most of the hippocampus, removed bilaterally. In addition to exhibiting severe anterograde amnesia, H.M., also appears to be insensitive to interoceptive states such as hunger and thirst. For example, in one study, H.M. consistently rated his hunger at about 50 on a scale ranging from 0 to 100, regardless of whether the rating was made immediately before or after a normally scheduled meal [104]. H.M was also reported to eat a second full meal that was offered only minutes after he finished a comparable first meal, which he could not remember. Rozin et al. [105] suggested that the inability to remember when his last meal occurred and how much he consumed might have contributed to H.M.s excessive eating. To test this hypothesis, Rozin recorded the eating behavior and hunger ratings of two densely amnesic patients with brain damage similar to that sustained by H.M. Also, like H.M., these patients had no memory of meals that they had just eaten. Rozin found that both patients rapidly consumed a second meal that was presented 10–30 min after they completed a first meal, and that they usually began to consume a third meal that started 10–30 min after the second meal. Unlike H.M., eating led to consistent decreases in hunger ratings for one patient and to inconsistent decreases for the other. However, the magnitudes of the decreases were smaller for both patients than for control subjects that had normal memory of meal-taking. These results suggest that these amnesic patients were, to some extent, able to detect changes in interoceptive stimulation that was produced by eating, but were largely unable to use these cues to inhibit their ingestive behavior.

This deficit may be secondary to the effects of hippocampal damage on memory. Higgs [106] assessed the effects of memory for a recent meal on subsequent food intake in humans with presumably normal memory ability. In this study, food intake was recorded during a test meal that was offered 2–5 h after the subjects, all non-dieting females, ate a normal lunch. Intake for subjects that were asked to think for 5 min at the time of testing about what they ate for lunch that day was suppressed during the test meal compared to subjects that were not given those recall instructions. Higgs suggested that the ability to inhibit a current bout of eating may be enhanced by the memory of eating a satiating meal 2 h earlier. Presumably, such memories were unavailable for H.M. and the patients studied by Rozin et al.

The finding that humans with damage that includes the hippocampus are less able than normal people to suppress food intake following a regular meal suggests that the hippocampus may be especially involved with utilizing satiety signals to inhibit eating behavior. The results of a recent fMRI study provide support for this interpretation. DelParigi et al. [107] measured changes in regional blood flow in people who were obese, postobese (i.e., people who were once obese, but were maintaining normal weight at the time of the experiment) and lean people with no history of obesity, after tasting and consuming a "satiating amount" of a liquid meal. The pattern of fMRI activity produced by merely tasting the liquid meal differentiated obese from both groups of lean individuals but did not involve differential activation of the hippocampus. In contrast, consuming a satiating amount of the liquid meal resulted in clear decreases in regional blood flow in the posterior hippocampus for both obese and postobese subjects but not for subjects who had never been obese. The authors concluded that obesity is characterized by abnormal activity in the hippocampus in response to a satiating meal, and that this pattern of neural activity persists in postobese individuals—people who can be considered at high risk for relapse. The authors suggested that the hippocampus contributes to the control of food intake regulation, and that this control is altered in both currently and formerly obese people.

4.2. The hippocampus and food intake regulation in rats

Rats with hippocampal damage far more selective than that sustained by H.M. also show abnormalities related to the control of their feeding behavior. Davidson and Jarrard [108] assessed the effects of ibotenate lesions of the hippocampus on the amount of food consumed daily, on appetitive food hopper approach behavior, and on general activity. All rats had free access to food during the continuous 2-day test period. Rats without a hippocampus showed significantly more appetitive behavior (as indexed by their tendency to make contact with a wire mesh grid that covered the food hopper) and significantly more general behavioral activity (as monitored by an ultrasonic recording device) than did intact controls. The mean amount of food consumed on each day of testing was greater, but not significantly so, for lesioned compared to control animals. This basic pattern of findings was confirmed and extended in a study by Clifton et al. [109]. In their experiment, food pellets were dispensed, one at a time into a food cup, with a new pellet being delivered when the previous pellet was removed, allowing precise determination of parameters such as meal size, meal frequency, and inter-meal interval. The results showed that, relative to sham-lesioned controls, the average meal size for rats with neurotoxic lesions of the hippocampus decreased by approximately half, whereas the number of daily meals increased by about 2.5 times following the lesion. As was reported by Davidson and Jarrard, rats with hippocampal lesions ate more, but not significantly more than controls.

Subsequent research showed that increased food cup approach on the part of hippocampal-lesioned rats was probably not a secondary effect of increased general behavioral activity, but rather that increased general activity was more likely to be a consequence of a heightened tendency to approach the food cup. Consider the results shown in Fig. 3, which come from a study conducted in our laboratory (see [110]). The general activity levels of rats with (Hip) and

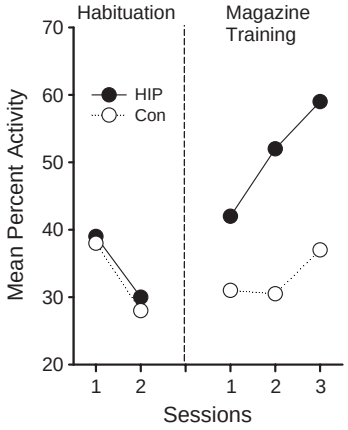

Fig. 3. Effects on hippocampal lesions on behavioral activity prior to and after the beginning of food presentations. General activity of rats with IBO lesions of the hippocampus did not differ significantly from that of controls during habituation training (left panel) which took place prior to presentation of food, but was significantly higher than that of controls after food reinforcement was introduced during magazine training (right panel).

without (Control) IBO lesions of the hippocampus, as measured by a computerized infrared monitoring system, are shown for five 20-min sessions. The first two sessions (left panel) were habituation sessions that took place prior to the presentation of food reward in the test apparatus. During these sessions, the behavioral activity of the lesioned and nonlesioned rats did not differ. The finding of no difference in general behavioral activity as a function of hippocampal damage agrees with other reports (e.g., [111,112]). In contrast, the right panel of Fig. 3 shows that hippocampal-lesioned rats began to show much greater behavioral activity compared to controls after the beginning of intermittent delivery (one 45-mg pellet every 2-min on average) of food pellets. Benoit et al. [68] later found that rats with selective ibotenate lesions of the hippocampus exhibited greater behavioral activity than intact controls largely as an increasing function of the number of food rewards that had been presented in the place where activity was measured. In contrast, activity levels in a novel context did not depend on lesion condition. The available findings indicate that hippocampal damage impairs the ability to inhibit both general behavioral activity and appetitive responses in the presence of cues that are associated with food, but does not have a strong, nonspecific activating effect on behavior when food cues are absent.

4.3. Hippocampal damage and the utilization of energy state signals by rats

Like the patients (described above) with temporal lobe damage that extends outside of the hippocampus, rats with damage confined to the hippocampus are also impaired in utilizing their interoceptive state signals. For example, Davidson and Jarrard [108] reported that, unlike intact controls, rats with ibotenate lesions of the hippocampus were unable to solve a nonspatial discrimination problem in which internal stimuli produced by 24-h food deprivation and by a 24-h period with free access to food served as discriminative signals for shock. Compared to controls, the rats with hippocampal damage showed similar levels of conditioned responding when under their reinforced level of food deprivation, but were unable to inhibit conditioned responding under their nonreinforced food deprivation condition. These same animals showed no deficit in learning to use auditory cues as simple discriminative stimuli, indicating that the impaired performance based on deprivation cues was not the result of a general deficit in the ability to solve discrimination problems or reduced effectiveness of the reinforcing stimulus that was used during training. Hock and Bunsey [113] obtained a similar pattern of impaired deprivation discrimination performance by rats with lesions that were confined to either the dorsal or the ventral portions of the hippocampus.

More recently, Kennedy and Shapiro [114] showed that the ability of rats to use their hunger and thirst cues to solve a nonspatial discrimination problem for food and water rewards depended on the hippocampus. This study is of special interest because (a) rats used their state cues to determine when external cues would be followed by appetitive, rather than aversive reinforcers; (b) the rats were trained to criterion on the deprivation state discrimination problem before hippocampal surgery was performed and (c) a series of probe tests showed that hippocampal surgery did not alter the ability to select and consume rewards (food or water) that were appropriate to the rat's current deprivation condition (hunger or thirst). This finding suggests that although hippocampal damage interfered with discrimination performance based on learning about interoceptive deprivation cues, this damage did not reduce the ability of rats to detect either the orosensory or postingestive consequences of ingestion.

4.4. Hippocampal damage and body weight in rats

The results discussed in the preceding sections show that damaging the hippocampus substantially increases food intake by humans, and markedly increases the performance of learned appetitive behaviors by rats. We recently assessed the effects of selective lesions of the rat hippocampus on both food intake and long-term weight gain. Previous studies have provided some evidence that rats with hippocampal damage eat more, but little evidence that rats gain more weight than controls (e.g., [108,109,115]). However, these studies used relatively short measurement periods (2–20 days) that often began immediately post-surgery and/or used nonselective lesion techniques (electrolytic, aspiration) that typically leave some parts of the hippocampus intact, damage extrahippocampal structures and fibers of passage, and produce substantial nonspecific behavioral activation that could alter energy intake and utilization.

To remedy these problems, we gave our rats selective IBO lesions that confined damage to the hippocampus, spared fibers of passage, and that reduced nonspecific effects on behavior. We also noted that a marked reduction in body weight occurs immediately following hippocampal surgery. However, IBO-lesioned rats exhibited gradual weight regain at a rate that enabled them to achieve and begin to exceed control weight

levels within a period of 20–30 days. This outcome suggested that recovery from the nonspecific effects of surgery could obscure the effects of removing hippocampus per se when food intake and body weight is measured for only a relatively short postsurgical period.

Our study (see [116]) attempted to control these potential problems by measuring the effects of selective IBO lesions of the rat hippocampus on food intake and body weight gain over an extended period of postsurgery. Furthermore, these effects were measured for hippocampal lesioned and control rats that were matched not only in terms of their pre-operative body weight, but also with respect to postoperative weights that were achieved following recovery from surgery. This matching procedure was used to reduce the possibility that changes in eating or body weight observed in postsurgery were influenced by recovery from any general behavioral depressive aftereffects of surgery that are not specific to the control of intake regulation. All rats were given ad lib access to food throughout testing. Under these conditions, we found that rats without a hippocampus ate significantly more (see Fig. 4) and gained significantly more weight (see Fig. 5) during the course of the 36-day test period than did controls (note that these data were collected at 48-h intervals).

At the end of this test phase we compared the sensitivity of IBO-lesioned rats and controls to the intake suppressive effects of exogenous CCK. All rats were injected, on two test days, with cholecystokinin (CCK-8, 8 μg/kg, ip) and with an equal volume (1 ml/kg) of isotonic saline. Treatment order was counterbalanced across surgical conditions. The rats were fasted for 24 h prior to each test, with one 24-h period with free access to food intervening between test sessions. Intake of normal chow was assessed at the end of two 30-min periods (0–30 min; 30–60 min) beginning for each rat immediately after injection. Although CCK suppressed intake equally well for hippocampal-lesioned and control rats during the first 30 min of testing, rats without a hippocampus ate significantly more than controls over the second 30 min of testing. No significant differences between rats with hippocampal lesions and controls were observed during either the first or second 30-min test periods following injection with saline. These results indicate that removing the hippocampus may make rats less sensitive to the intake suppressive effects of CCK. These effects of hippocampal lesions on food intake and body weight are of small magnitude compared to the hyperphagia and weight gain shown by rats with lesions of the ventromedial hypothalamus (see [38]). However, the gradual accumulation of weight in rats with hippocampal lesions is reminiscent of the gradual weight gain exhibited by OLETF rats over their lifetime [117]. Moreover, one can argue that small, consistent, elevation in caloric intake leading to gradual increments in weight gain is similar to the gradual fattening of the human population (approximate average of 0.5–1.0 kg/year weight gain over 10 years) that characterizes the current rise in the incidence of overweight and obesity [118].

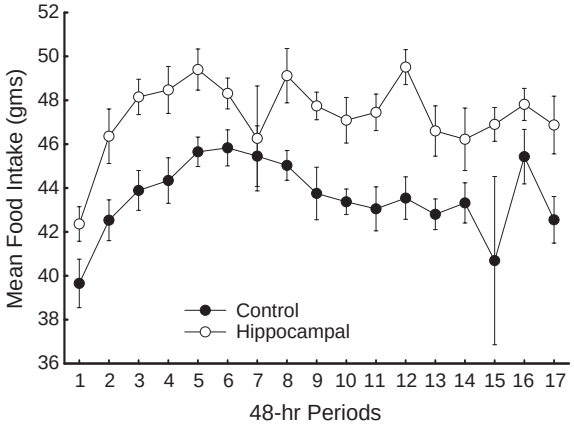

Fig. 4. Average food intake for rats with hippocampal lesions and controls. Amount eaten was measured once every 48 h for 36 days beginning after both groups of rats achieved comparable postsurgery body weights. Mean weights at baseline=319 g for hippocampal lesioned rats and 322 g for controls.

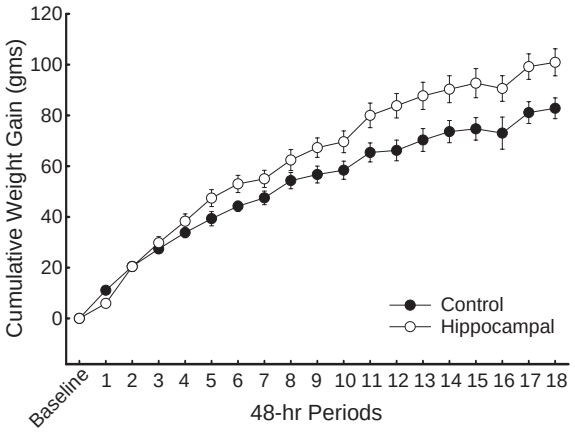

Fig. 5. Cumulative body weight gain for rats with hippocampal lesions and controls. Body weight gain was calculated once every 48 h for 36 days. Mean weight at baseline=319 g for hippocampal lesioned rats and 322 g for controls.

4.5. Dietary factors and hippocampal function

The finding that selective and complete removal of the hippocampus leads to increased food intake and weight gain in rats helps to establish a role for the hippocampus in the regulation of food intake. However, this finding may add little to understanding on what is currently causing people to become overweight and obese outside of the laboratory, unless one can identify environmental changes that are linked to excess food intake and weight gain that can also impair hippocampal functioning. As noted earlier, recent society-wide trends toward obesity have been accompanied by increased availability of low-cost, highly palatable, energy dense (e.g., high-fat) foods. Previous epidemiological (e.g., [119,120]) and experimental studies (e.g., [121–123]) have called attention to a possible relationship between intake of high-fat diets and reduced cognitive ability. However, intriguing new research is beginning to emerge which points to a mechanism that might explain how consumption of these types of foods can disturb cognitive processes.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family, which plays important roles in the

survival, maintenance and growth of many types of neurons [124,125]. BDNF influences the development and complexity of dendritic connections [126] in the cerebral cortex [127] and it is well documented that BDNF can protect neurons from insult or disease [128,129]. BDNF is expressed abundantly in the hippocampus, hypothalamus, and cerebral cortex and is involved with activity-dependent long-term potentiation [130–132], which is, as noted previously, a proposed cellular mechanism for memory formation. In this regard, the expression of BDNF is increased in the hippocampus, but not in the cerebellum, striatum, frontal, and middle or caudal neocortex of animals that learn a spatial memory task [131,133]. Furthermore, animals with reduced expression of hippocampal BDNF show deficits in spatial memory [134] whereas intrahippocampal infusions of BDNF have been reported to improve performance on spatial tasks (e.g., [135]). In addition, BDNF has been linked to energy regulation based on its ability to suppress weight gain produced by consuming a high-fat diet in mice with deficient melanocortin 4 receptor signaling [136].

The findings of a number of recent studies indicate that consumption of a diet high in saturated fat may interfere with learning and memory processes by reducing levels of hippocampal BDNF [137,138]. For example, Molteni et al. [137] gave rats a maintenance diet that was high in saturated fat and refined sugars. The composition of this diet was designed to be similar to the typical diet of most industrialized western societies. Rats that had as little as 2 months of experience with this experimental diet had significantly reduced levels of hippocampal BDNF compared to controls maintained on low-fat, high-carbohydrate chow. However, BDNF levels in the cortex did not differ between these two groups. Moreover, consumption of the experimental diet was also accompanied by significant reductions in hippocampal LTP and by significantly impaired performance in the Morris water maze, a spatial learning task that is widely held to be dependent on the hippocampus.

This study is important because it provides evidence that (a) even relatively short-term consumption of a highly palatable, energy-dense, high-fat diet alters a neurochemical process that impacts hippocampal neural functioning; and (b) this interference leads to impaired performance on a learning and memory task that has been shown to depend on the structural integrity of the hippocampus. Although the weights of the rats on each diet were not reported, it is highly likely that rats on the experimental diet also ate more and gained more weight than controls, a finding that would reflect an impaired ability to maintain normal energy balance. More recently, Baran et al. [139] observed dendritic atrophy in the hippocampal CA3 cells of rats that were maintained for as little as 3 weeks on a high-fat diet under conditions of psychosocial stress (e.g., crowded housing). These findings could further illuminate the mechanisms by which high-fat diets disrupt hippocampal functioning.

4.6. Summary

A wide variety of evidence suggests that the hippocampus may contribute to the control of energy balance. Both neuroanatomical and neurohormonal pathways connect the hippocampus to other brain regions (e.g., arcuate nucleus, NTS) that have been identified as important substrates for intake regulation. Findings that neuropeptide satiety (e.g., CCK) and adiposity (e.g., leptin, insulin) signals also play a role in the performance of hippocampal-dependent learning and memory functions encourage speculation that the effects of these neuropeptides on food intake might be based, in part, on their effects on behavioral inhibition processes that are mediated by the hippocampus. Brain damage in humans that includes the hippocampus, as well as more selective neurotoxic hippocampal lesions in rats have been shown to disrupt the ability of interoceptive state signals to modulate behavior, and are associated with increased appetitive and consummatory responding. Evidence that hippocampal activity involved with processing satiety information is altered in obese and formerly obese people has been provided by fMRI studies. Recent findings obtained in our own laboratory show that rats without a hippocampus gain more weight and eat more food than intact controls. Rats with the hippocampus removed also exhibited reduced sensitivity to short-term meal termination signals produced by CCK. Finally, recent studies show that consumption of a diet rich in fat and processed sugar can interfere with performance on at least some hippocampal-based learning and memory problems, and these deficits have been tied to the effects of these diets on hippocampal levels of BDNF.

Next, we consider the implications of these findings in conjunction with data summarized earlier showing that (a) food intake regulation is likely to involve certain forms of inhibitory learning and (b) the hippocampus is a substrate for the acquisition and utilization of these forms of inhibitory control. This analysis provides the foundation for a novel model of obesity.

5. A “Vicious Circle” model of obesity

Fig. 6 depicts what might be termed a “Vicious Circle” model of obesity. This model starts with the conventional assumption that an “unhealthy diet” is one that includes too many highly palatable foods that are rich in saturated fat and refined sugar. However, in the Vicious Circle model, this diet is not considered to be unhealthy for the conventional reasons (e.g., increased risk of cardiovascular disease, hypertension, etc.). This diet is considered unhealthy to the extent that consuming it interferes with or degrades a critical hippocampal

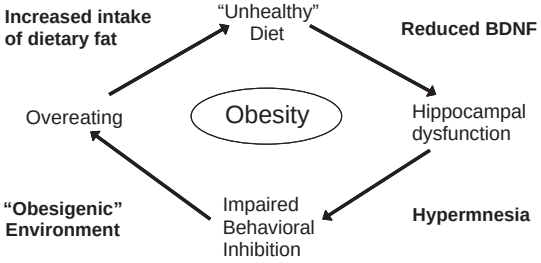

Fig. 6. A hypothetical “vicious circle” model of overeating and weight gain. (See text for explanation.)

function. This function involves the ability to inhibit the activation of the memories of food or of the rewarding consequences of eating. If this inhibitory function is disturbed, these memories and the environmental cues that retrieve them will have increased power to evoke appetitive responses that are instrumental to obtaining and consuming food. Based on the assumption that the inhibition of these memories and the responses they trigger is normally strongest under conditions of positive energy balance, weakening of this type of control would result in energy intake in excess of energy needs (i.e., overeating).

The types of foods that are most likely to be approached and over-consumed are those that are associated with the most numerous and salient environmental retrieval cues (e.g., are widely available, highly advertised), that excite memories of highly rewarding oral (i.e., are highly palatable) and post-ingestive (e.g., produce quick corrections of mild negative energy balance) sensory consequences. Within the Vicious Circle model, these foods may be the same widely available, highly marketed, highly palatable, energy-dense products that give rise to hippocampal dysfunction in the first place. This set of circumstances could provide the basis for a potential "vicious circle" of intake leading to reduced inhibitory control producing increased intake, resulting in greater failure of inhibitory control, etc., all of which are antecedent to the gradual fattening of population.

The Vicious Circle model outlines a mechanism whereby changes in the food environment that began many years ago could gradually alter brain functioning to weaken the regulatory control of energy intake. A number of important details of this model have already been mentioned. For example, recent reports show that diets high in fat and processed sugar reduce hippocampal BDNF and that reduced hippocampal BDNF alters at least some hippocampal-dependent cognitive processes. In addition, receptors for important short-term (CCK) and longer term (leptin, insulin) intake inhibiting neuropeptides are not only abundant in the hippocampus, but have also been shown to influence memory functions that are thought to rely on hippocampus. Impaired hippocampal sensitivity to the intake suppressive effects of one or more of these signals could promote food intake. Furthermore, a variety of research findings and several current theoretical formulations have already suggested that one of these hippocampal-dependent memory functions is to inhibit activation of highly salient or prepotent memories, thereby contributing to the inhibition of the behavioral responses they evoke. Thus, links between the hippocampus and behavioral inhibition have already been identified. Moreover, there is substantial evidence from human and animal studies that disrupting hippocampal function reduces the ability to inhibit eating and appetitive behavior and to regulate body weight.

6. Conclusions

It is often said that people who overeat and become overweight or obese lack the ability or will-power to control their eating behavior. Many attribute this lack of control to an environment where food is abundantly available and where people are constantly reminded about the pleasures of eating it. These cues may be too much to resist. There is good reason to believe that learning about environmental cues that have been associated with the rewarding consequences of eating is an important contributor to caloric intake in excess of regulatory needs. Research reported in this issue (Balleine; Holland and Petrovich; Kelley) provides important new findings about the brain substrates that underlie the potential incentive value, reward, and habit mechanisms which contribute to the excitatory control of conditioned feeding behaviors.

In the present paper, we attempted to expand on this basic conceptualization in several ways. We proposed that: (1) regulatory control of food intake depends not only on excitatory, but also on concurrent inhibitory learning about the relationship between environmental food cues and rewarding postingestive events; (2) the presence and absence of physiological satiety signals modulate whether food cues excite or inhibit the memory of these rewards; (3) the modulatory power of satiety signals emerges as a result of their being embedded in a "natural" Pavlovian conditional discrimination or negative occasion setting problem; (4) the hippocampus is at least part of the neural substrate for the type of inhibitory learning on which occasion setting is based.

Finally some researchers attribute the continuing trends toward increased eating, body weight, and obesity to a biological system of intake control that has been contra-prepared by evolution to meet the regulatory challenges posed by the current food environment. The rapid increase in overweight and obese people in the general population has led others to question whether or not caloric intake is even a regulated parameter, at least in environments where food is readily available (e.g., Mattes, this issue). The present paper retains the idea that caloric intake is under regulatory control (also see Woods, this issue). But rather than attribute the current weakness in energy regulation solely to genetic factors, we offer the alternative possibility that recent changes in the food environment have diminished the ability of the hippocampus, and perhaps other brain areas, to perform higher order cognitive inhibitory control functions.

It may be that our obesigenic environment also interferes with these inhibitory control functions in other ways. For example, intake regulation may depend in part on the ability to use orosensory stimuli to predict nutritive or caloric outcomes (see Swithers and Davidson, this issue [140–142]). Degrading this predictive relationship by intermittent exposure to food cues that are not good predictors of calories or nutrients would presumably make it more difficult for animals to use their satiety signals to set the occasion for when a given food cue will or will not be followed by rewarding postingestive stimulation. This could interfere with the ability of satiety cues to function as negative occasion setters. The possibility that exposure to aspects of the current food environment might impair energy regulation by interfering with the neural substrates that underlie negative occasion setting or by disrupting negative occasion setting itself may provide a useful alternative framework for approaching the continuing problem

of excess food intake and body weight gain in the human population.

Acknowledgements

The authors thank Andrea Tracy, Mamta Behl, Stephen Benoit, Debbie Clegg and Jim Nairne for comments and discussion that helped to develop many of the ideas presented in this paper. We also thank Jennie Mak for technical assistance with the preparation of this manuscript. Funding in support of this work was provided by Grants R01 HD44179 and R01 HD29792 from the National Institutes of Health to TLD.

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